

Infection for *Mycobacterium tuberculosis* and Nontuberculous Mycobacteria in the HIV/AIDS Patients

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1. Introduction

Tuberculosis (TB) is a disease also known as consumption, wasting disease, and the white plague, it has affected humans for centuries. Until the mid-1800s, people thought that tuberculosis, or TB, was hereditary. They did not realize that it could be spread from person to person through the air. Also, until the 1940s and 1950s there was no cure for TB. For many people, a diagnosis of TB was a slow death sentence¹⁻⁴.

In 1865 a French surgeon, Jean-Antoine Villemin, proved that TB was contagious, and in 1882 a German scientist named Robert Koch discovered the bacteria causes TB, denominated as *Mycobacterium tuberculosis*. Yet half a century passed before drugs were discovered that could cure TB, until then, many people with TB were sent to sanatoriums, special rest homes where they followed a prescribed routine every day. A breakthrough came in 1943, an American scientist, Selman Waksman discovered a drug that could kill TB bacteria. Between 1943 and 1952, two more drugs were found, after these discoveries, many people with TB were cured and the death rate for TB in the United States dropped dramatically, and fewer and fewer people got TB⁵.

A global health emergency^{6,7}:

- Someone in the world is newly infected with TB bacilli every second.
- Overall, one-third of the world's population is currently infected with the TB bacillus.
- 5-10 % of people who are infected with TB bacilli become sick or infectious at some time during their life.

TB program activities, reinforced by successful chemotherapy, resulted in a pronounced reduction of infection and death rates. The disease became greatly controlled but it never quite disappeared. Then, in around 1985, cases of TB began to rise again in industrialized countries. Several inter-related forces drove this resurgence, including increase in prison populations, homelessness, injection drug use, crowded housing and increased immigration from countries where TB continued to be endemic. Above all, the decline in TB control activities and the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic were two major factors fuelling each other in the re-emergence of TB. People with HIV and TB infection are much more likely to develop TB. The HIV/AIDS epidemic has produced a devastating effect on TB control worldwide. While one out of ten

immunocompetent people infected with *M. tuberculosis* will fall sick in their lifetimes, among those with HIV infection, one in ten per year will develop active TB. In developing countries, the impact of HIV infection on the TB situation, especially in the 20-35 age groups, is overwhelming. While wealthy industrialized countries with good public health care systems can be expected to keep TB under control, in much of the developing world a catastrophe awaits. In poorly developed countries, TB remains a significant threat to public health, as incidences remain high, even after the introduction of vaccination and drug treatment. The registered number of new cases of TB worldwide roughly correlates with economic conditions: highest incidences are seen in the countries of Africa, Asia, and Latin America with the lowest gross national products. Supervised treatment, including sometimes direct observation of therapy (DOT), was proposed as a means of helping patients to take their drugs regularly and complete treatment, thus achieving cure and preventing the development of drug resistance⁵⁻⁷.

2. Transmission and pathogenesis

TB is spread from person through the air. When a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings, droplet nuclei containing *Mycobacterium tuberculosis* are expelled into the air. Depending on the environment, these tiny particles (1-5 microns in diameter) can remain suspended in the air for several hours. If another person inhales air containing droplet nuclei, transmission may occur. The probability that TB will be transmitted depends on these factors^{4,5}:

- The infectiousness of the person with TB (the number of organisms expelled into the air).
- The environment in which exposure occurred.
- The duration of exposure and the virulence of the organism.

The best way to stop transmission is to isolate patients with infectious TB immediately and start effective TB therapy. Infectiousness declines rapidly after adequate therapy is started, as long as the patient adheres to the prescribed regimen. Persons at the highest risk of becoming infected with *Mycobacterium tuberculosis* are close contacts, the persons who had prolonged, frequent, or intense contact with a person with infectious TB. Close contacts may be family members, roommates, friends, coworkers, or others. Data collected by CDC since 1987 show that infection rates have been relatively stable, ranging from 21-23% for the contacts of infectious TB patients⁶⁻⁹. Some people with infection develop TB disease. This disease develops when the immune system cannot keep the tubercle bacilli under control and the bacilli begin to multiply rapidly. The risk that TB disease will develop is higher for some people than for others^{3, 10-12}. Among contacts of persons with drug-resistant TB, infection rates seem to be similar. However, because they may have a poor response to treatment persons with drug-resistant disease are often infectious for longer periods and therefore have the potential to infect more contacts¹⁰⁻¹³.

Extra pulmonary TB is rarely contagious; however, transmission from extrapulmonary sites has been reported during aerosol-producing procedures, such as autopsies and tissue irrigation¹⁴⁻¹⁶.

3. Pathogenesis

The tubercle bacilli that alveoli are ingested by alveolar macrophages, the majority of these bacilli are destroyed or inhibited. A small number multiply intracellularly and are released

when the macrophages die. These bacilli can spread through the lymphatic channels to regional lymph nodes and then through the bloodstream to more distant tissues and organs, including areas in which TB disease is most likely to develop: the apices of the lung, the kidneys, the brain, and bone. Extracellular bacilli attract macrophages from the bloodstream. The immune response kills most of the bacilli, leading to the formation of a granuloma. At this point the person has TB infection, which can be detected by using the tuberculin skin test. It may take 2-10 weeks for the infected person to develop a positive reaction to the tuberculin skin test. Immune responses soon develop to kill the bacilli. Within 2-10 weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further spread^{4, 17-19}.

In persons infected with *Mycobacterium tuberculosis* but that don't have TB disease cannot spread the infection to other people. TB infection in persons who does not have TB disease is not considered a case of TB and referred to as "latent TB infection". In some persons, TB bacilli overcome the defenses or the immune system and begin to multiply, resulting in the progression from TB infection to TB disease. This process may occur soon after or many years after infection. Some study demonstrated that approximately 5% of person who have been infected with *Mycobacterium tuberculosis* will develop TB disease in the first year or two after infection and another 5% will develop disease some time later in life. Recent infection (with the past 2 years) with *Mycobacterium tuberculosis* is therefore an important risk factor for progression to TB disease and in approximately 10% of persons with normal immune system who are infected with *Mycobacterium tuberculosis*, TB disease will develop at some point⁵⁻⁷.

Some medical conditions increase the risk that TB infection will progress to disease. Some studies suggest that the risk is mayor in immunosuppressed patients, for example persons with Diabetes mellitus, prolonged therapy with corticosteroids, immunosuppressive therapy, certain types of cancer, severe kidney disease, injection of illicit drugs, and infection with Human Immunodeficient Virus (HIV)^{2,3,12}.

TB disease most commomly affects the lung, 73% of TB cases are exclusively pulmonary, and however, TB is a systemic disease and may also commonly occur in the following ways; as pleural effusion in the central nervous, lymphatic, or genitourinary systems, as disseminated disease (military TB). Also the infection for *Mycobacterium tuberculosis* can occur in the other body sites; in the breast, skin, or peritoneum^{16,20-23}. Extrapulmonary TB is more common in immunosuppressed persons and in young children; meningoencephalitis TB, lymphatic TB and military disease are particularly common in immunosuppressed persons, in some case the extrapulmonary TB is often accompanied by pulmonary TB^{3, 8, 16-23}.

4. Epidemiology of TB

TB infection is one of the most common infections in the world. It is estimated that 30-60% of adults in developing countries have TB infection. Annually about 8-10 million people develop TB disease and 2-3 million people die of the disease. TB disease is the leading cause of death due to infectious disease around the world^{24, 25}. When the health department learns about a new case of TB, it should take steps to ensure that the person receives appropriate treatment. Is very important that the health authorities should also start a contact investigation, this means interviewing a person who has TB disease to determinate

who may have been exposed to TB, this person are screened for TB infection and disease ^{8, 26-28}.

In order to the decrease in the number of TB cases reported annually is very important to comply three factors ²⁹:

- To increase federal resources for TB control and other public health efforts.
- To improve prevention and TB control programs in state and local health department.
- To Increase attention to ensuring that patients complete drug therapy through directly observed therapy (DOT).

In the control of TB disease is also important to know the Groups at High Risk for TB ^{29, 30}:

People at Higher Risk for Exposure or Infection:

- Close contacts of people with infectious TB disease.
- People born in areas of the world where TB is common.
- Elderly people.
- Low-income groups with poor access to health care, including homeless people.
- People who inject illicit drugs.
- People who live or work in residential facilities (Example: nursing correctional facilities).
- Other people who may be exposed to TB on the job.
- People in other groups as identified by local public health officials.

People at Higher Risk for TB disease:

- People with other medical conditions that can increase the risk for TB.
- People recently infected with *Mycobacterium tuberculosis*.
- People with chest x-ray suggestive of previous TB disease.
- People who inject illicit drugs.
- People with HIV infection.

Infection with HIV makes people susceptible to rapidly progressive tuberculosis; over 10 millions peoples are infected with both HIV and *Mycobacterium tuberculosis* ⁸.

TB in Children:

The occurrence of TB infection and disease in children provide important information about the spread of TB in homes and communities. When a child has TB infection or disease is important to learn if ²⁹⁻³¹ :

- Recent TB transmission.
- Other adults and children in the household or community have probably been exposed to TB; if they are infected, they may develop TB disease in the future.

4.1 Drug-resistant tuberculosis

Drug-resistant TB is transmitted in the same way as drug-susceptible TB. The earlier outbreaks of multidrug-resistant (MDR) TB support the findings that drug-resistant TB is no less infectious than drug-susceptible TB, although prolonged periods of infectiousness that often occur in the patients with drug-resistant TB may facilitate transmission. Drug resistance was divided in two types; primary resistance and secondary or acquired resistance. Primary resistance develops in persons who are initially infected, with resistant organisms. Second resistance, or acquired resistance develops during TB therapy, either because the patient was treated with an inadequate regimen or because the patient did not take the prescribed regimen appropriately ^{27, 29, 32}. The MDR-TB are resistant to rifampicin and isoniazid drugs. Recently drug-resistant tuberculosis (XDR-TB) is defined as tuberculosis caused by a *Mycobacterium*

tuberculosis strain that is resistant to at least rifampicin and isoniazid among the first-line antitubercular drugs (MDR-TB) in addition to resistance to any fluoroquinolones and at least one of three second-line drugs, namely amikacin, kanamycin and/or capreomycin. Current studies have described XDR-TB strains from all continents. Worldwide prevalence of XDR-TB is estimated in 6.6% in all the studied countries among MDR-TB strains. The emergence of XDR-TB strains is a reflection of poor tuberculosis management, and controlling its emergence constitutes an urgent global health reality and a challenge to tuberculosis control activities in all parts of the world, especially in developing countries and those lacking resources and as well as in countries with increasing prevalence of HIV/AIDS³²⁻³⁴.

5. Diagnosis of tuberculosis

The systemic symptom of Tuberculosis include fever, chills, night sweats, appetite loss, weigh loss, and easy fatigability, the symptoms of pulmonary TB are productive and prolonged cough (>14-21 week), chest pain and in some case the patient present hemoptysis. It is important to ask persons suspected of having tuberculosis about their history of TB exposure, infection, or disease. The clinicians may also contact the local health department for information about whether a patient has received tuberculosis treatment in the past, if the drug regimen was inadequate or if the patient may did not adhere to therapy, this disease may recur and may be drug resistant. Also is important to consider demographic factors; country of origin, age, ethnic or racial group and occupation, this factors may increase the patient's risk for exposure to TB or drug-resistant TB disease. Clinicians should determinate whether the patient has medical conditions, especially HIV infection, because this infection increases the risk for TB disease. All patients who do not know their current HIV status should be referred for HIV counseling and testing^{26, 27}.

The tuberculin skin test and the chest radiography, are two probes that help in the diagnostic for TB disease. Tuberculin skin testing useful for²⁹:

- To examine a person who is not ill but may be infected with *Mycobacterium tuberculosis*, such as a person who has been exposed to someone who has TB. This test is the only way to diagnose tuberculosis infection before it has progressed to tuberculosis disease.
- To determine how many people in group are infected with *Mycobacterium tuberculosis*.
- To examine person who has symptoms of TB.

A negative reaction to the tuberculin skin test does not exclude the diagnosis of TB, especially for patients with severe TB illness or infection with HIV. Some persons may not react to the tuberculin skin test if they are tested too soon after being exposed to the infection. Generally it takes 2-10 week after infection for a person to develop an immune response to tuberculin. In children younger than 6 months of age may not react to the tuberculin skin test because their immune systems are not yet fully developed³².

5.1 Chest radiography

The chest radiography is for:

- To detect abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe.
- To detect atypical images in immunosuppressed persons an in HIV-positive persons.

In HIV-infected persons, pulmonary TB may appear in the chets radiograph. For example; TB disease may cause infiltrates without cavities in any lung zone, or it may cause

mediastinal or hilar lymphadenopathy with or without accompanying infiltrates and/or cavities. In HIV-positive persons, almost any abnormality on a chest radiograph may indicate TB. In fact, the radiograph of an HIV-positive person with TB disease may even appear entirely normal. Abnormalities on chest radiographs may be suggestive of, but are never diagnostic of TB. However, chest radiographic may be used to rule out the possibility of pulmonary TB in a person who has a positive reaction to the tuberculin skin test and no symptoms of disease ^{29, 31, 32, 34}.

Summarizing the possibility of TB should be considered in persons who have these symptoms, person suspected of having this disease should be referred for a medical evaluation, which should include a medical history, a physical examination, a Mantoux tuberculin skin test or tuberculosis purified protein derivate (PPD) skin test, a chest radiograph. Also, it is very important any appropriate bacteriologic or histological examinations in this patients, principally in all immunosuppressed patients, of course including the HIV patients ²⁹.

Person with symptoms of TB pulmonary disease should have at least three sputum specimens examined by smear and culture. The best way would be to get serial specimens collected early in the morning on 3 consecutive days. A health care worker should be prepared and directly supervise at least during the first time sputum collection. This person should be properly instructed in how to produce a good specimen, the patients should be informed that sputum is the material brought up from the lungs and that mucus from the nose or throat and saliva are not good specimens ^{35, 36}.

Recommendations for Specimen Collection:

- Get 3 sputum specimens for smear examination and culture.
- In persons unable to cough up sputum, induce sputum, bronchoscopy or gastric aspiration.
- Before chemotherapy and drug therapy is started.
- To use clean, sterile, one-use, plastic, disposable containers that have been washed with dichromate sulfuric acid and sterilized.
- To transport specimens to the laboratory as soon as possible.

5.2 Laboratory examination

Detection of acid-fast bacilli (AFB) in stained smears examined microscopically may provide the first bacteriologic of TB. The traditional method for to detect AFB is the Ziehl-Neelsen coloration, it is a method more economic. There are other methods that increased sensitivity as fluorescent methods. Smear examination is an easy and quick procedure, because the results should be available within 24 hours of specimen collection. However, smear examination permits only the presumptive diagnosis of TB because many TB patients have negative AFB smears. The sensitivity of smear examination may be reduced if the directed inflammatory response and relative absence of cavitory lesions results in fewer organisms expectorated in sputum. There has been concern that the utility of sputum acid-fast smears may be reduced in HIV-infected populations ^{36, 37}.

5.3 Extrapulmonary TB disease

This disease is not taken into account as causative agent of an extrapulmonary disease because the chest radiography is normal or tuberculin skin test is negative, or both. Mycobacteria may infect almost any organ in the body, the laboratory should expect to

receive a variety of extrapulmonary specimens: aseptically collected body fluids, surgically excised tissue, aspirated or draining pus, and urine. Others aseptically collected specimens are the body fluids as spinal, pleural, pericardial, synovial, ascetic, blood, pus, and bone marrow are aseptically collected by the physician using aspiration techniques or surgical procedure. Acid-fast bacilli may be difficult to isolate from some of these specimens because they often are diluted by the large fluid volume^{16-19, 37-39}.

The identification of TB can be done by traditional culture materials include egg-based solid media, such as Löwenstein-Jensen medium, and synthetic solid media as Middlebrook 7H10 and 7H11 agars. The identification depends on the visualization of mycobacterial colonies and is limited by the slow growth rate of these organisms. A major advance in laboratory diagnosis of TB has been the development of systems based on detecting growth in liquid media with the use of radiometric methods as Bactec System. In this, the medium contains palmitic acid labeled with carbon-14. The metabolism of this fatty acid by growing mycobacteria liberates radioactive carbon dioxide, periodic sampling of the gasses in the culture-containing flask permits rapid detection of mycobacterial growth⁴⁰⁻⁴¹.

Species identification was accomplished with biochemical test that often involved additional diagnostic delays. Others techniques, currently being evaluated in a number of clinical settings include identification based on chromatography techniques for the studies of some specific lipids present in the wall of *Mycobacterium*^{42, 43}. Also genetic probes are now availed for the identification of *Mycobacterium tuberculosis* and several other common mycobacterial species. These probes recognize species-specific sequences of ribosomal RNA. Theoretically, genetic probe as polymerase chain reaction (PCR), may permit diagnosis directly from patients specimens, eliminating the need for culture of organism. In practice, the utility of PCR has been limited by problems with the sensitivity and particularly, the specificity of results. In some laboratories, the sensitivity and specificity have been reported to exceed 85%. However, in several laboratories, false-positive rates ranged from 3% to 20%, and in one, 77% of positive results were false. In the last time the Genotype Mycobacteria Direct Assay (GTMD), a novel commercial assay based on nucleic acid sequence-based amplification technology, was evaluated for detection of *Mycobacterium tuberculosis* complex and some atypical mycobacterial species from clinical samples, and your sensitivity, specificity, positive predictive, and negative predictive were evaluated and these results were more better⁴⁴⁻⁴⁶.

6. Nontuberculous mycobacteria in the environment

Environmental opportunistic mycobacteria are those that are recovered from natural and human influenced environments and can infect and cause disease in humans, animals, and birds. Other names for these mycobacteria are nontuberculous, however, they cause tuberculous lesions, also other name is atypical mycobacterial, it distinguish from "typical" *Mycobacterium tuberculosis*, and them nontuberculous mycobacteria (NTM). The environmental opportunistic mycobacteria are normal inhabitants of natural waters, drinking water, and soils. They can be isolated from biofilms, aerosol, and dusts. The distribution of NTM and the incidence of disease caused by them is perhaps are not fully understood in most parts of the world. NTM are widely distributed in nature and have been isolated from natural water, rap water, tap water, and water used in showers and surgical solutions⁴⁷⁻⁵¹.

It is common observation that environmental mycobacteria cause disease in individuals who offer some opportunity due to altered local or systemic immunity. Chronic obstructive pulmonary diseases, emphysema, pneumoconiosis, bronchiectasis, cystic fibrosis, thoracic scoliosis, aspiration due to esophageal disease, previous gastrectomy and chronic alcoholism are some of conditions which have been linked to disease due to NTM. While the reasons may be less clear in conditions like adenitis in children, such factors may be quite obvious in other conditions like bronchiectasis, surgical procedures, injections, break in skin surface due to wounds and generalized immune deficiency states like AIDS, use of immunosuppressive agents as used in transplant patients, etc ^{50,51}.

6.1 Pathogenesis

The mechanisms of pathogenesis of NTM are not very clear and have not been adequately investigated. Very low CD4 counts and defective cytokine response have been linked to severe infections in AIDS patients ⁵⁰.

Nontuberculous mycobacteria have been reported to cause localized or disseminated disease depending on local predisposition and/or degree of immune deficit. In non-HIV patients, different NTM may cause localized pulmonary disease, adenitis, soft tissue infections, infections of joints and bones, bursae, skin ulcers and generalized disease in individuals like leukemia, transplant patients, etc. In AIDS patients the manifestations may range from localized to disseminated disease. Clinical features will include local organ specific signs and symptoms to persistent high grade fever, night sweats, anemia and weight loss in addition to nonspecific symptoms of malaise, anorexia, diarrhea, myalgia and occasional painful adenopathy ⁵²⁻⁵⁷.

7. Epidemiology of human infection with nontuberculous mycobacteria

The frequency of NTM pulmonary disease has been reported to be increasing on several continents. Changing patient populations, most notably from infection with HIV, have greatly increased the numbers of people at risk ⁵⁷⁻⁶⁰. Studies addressing the epidemiology of NTM infection may be broadly divided into three types: cutaneous delayed-type hypersensitivity to NTM antigens has been used to study large samples of people in many countries. These studies have the strength of providing information regarding simple infection in large groups of people but suffer from the lack of information regarding the prevalence of disease. Another drawback of this study type reflects the relatively poor specificity of the skin test, as well as overlap in reactivity among various Mycobacterial species. The second useful type of epidemiologic study of NMT infection includes investigations reviewing consecutive isolates from a mycobacterial laboratory. In the presence of adequate laboratory protocols to avoid contamination with environmental organisms, these studies provide unequivocal evidence of infection but have the obvious shortcoming of a lack of clinical data, preventing the assessment regarding the presence or absence of disease. The final and most useful study type combines information from the mycobacterial laboratory and the clinician's assessment ⁵⁵⁻⁶².

A true increase in rates of infection and disease could be related to the host, the pathogen, or some interaction between the two. Host changes leading to increased numbers of susceptibility could play an important role, with increased numbers of patients with inadequate defenses from diseases such as HIV infection, malignancy, or simply advanced

age. Many investigations have observed decreasing rates of TB concomitant with the increases in NTM. Finally, an interaction between the host and pathogen could involve a major increase in pathogen exposure or potential inoculum size⁶³⁻⁶⁷.

7.1 Clinical manifestations

Environmental opportunist or nontuberculous mycobacteria (NMT) include both slowly and rapidly growing. The range of infections caused by environmental opportunist mycobacteria is quite broad^{8, 51}.

7.2 Pulmonary infections

Mycobacterium avium-intracellulare complex (MAC) strains have been a major cause of pulmonary and other infections, principally in the HIV patients. MAC infections were commonly seen in chronic obstructive airway disease and in the in the geriatric patients too. *Mycobacterium kansasii* and *Mycobacterium scrofulaceum* have been considered an important cause of pulmonary infections. *Mycobacterium xenopi*, an unusual specie has been encountered as a pathogen in patients with other underlying lung diseases. Others species of slow grown as *Mycobacterium simiae* (*Mycobacterium habana*), *Mycobacterium szulgai*, *Mycobacterium malmoeense* and *Mycobacterium fortuitum* of rapid grown are other pathogens reported to be associated with pulmonary infections^{51, 65-68}.

7.3 Cutaneous infection

Mycobacterium szulgai, *Mycobacterium marinum*, *Mycobacterium ulcerans* and *Mycobacterium vaccae* have been reported to be a cause of skin infectious. *Mycobacterium marinum*, specie has been recognized as a causative organism of swimming pool granuloma or fish tank granuloma. It causes papular lesions in the extremities and may be confused with sporotrichosis. *Mycobacterium ulcerans* is established cause of buruli ulcer, *Mycobacterium vaccae* has also been reported to be a cause of skin infections⁵¹⁻⁵⁶.

7.4 Wound infection bone, joints and bursae and sepsis

Mycobacterium fortuitum causes pyogenic lesions in the soft tissue, joints, bursae and injection abscesses, while *Mycobacterium chelonae abscessus* is a well known cause of wound infections, a new related species *Mycobacterium immunogenum* has been recently been recognized as a cause of sepsis. *Mycobacterium marinum* also causes infections of bones, joints, tendon sheaths especially in AIDS patients. *Mycobacterium smegmatis*, and more recently *Mycobacterium wolinskyi* and *Mycobacterium thermoresistibile* have been reported to cause wound infection and also bacteraemia. *Mycobacterium terrae* complex (*Mycobacterium terrae*, *Mycobacterium nonchromogenicum* and *Mycobacterium triviale*) may be associated with mycobacterial disease. Also occasionally *Mycobacterium nonchromogenicum* and *Mycobacterium chelonae* have been identified as causes of acupuncture induced infections. *Mycobacterium septicum* a new rapidly growing species has been reported to be associated with catheter related bacteremia^{49, 51, 57, 58}.

7.5 Lymphadenitis

Infection of the submaxillar, cervical, inguinal or preauricular lymph nodes is the most common presentation of NTM lymphadenitis. The involved lymph nodes are generally unilateral (95%) and not tender⁵⁴⁻⁵⁷. The nodes may enlarge rapidly, and even rupture, with

formation of sinus tracts that result in prolonged local drainage. Other nodal groups outside of the head and neck may be involved occasionally. Distinguishing tuberculous from nontuberculous lymphadenitis is key because the former requires drug therapy and public health tracking, whereas the latter does not. A definitive diagnosis of NTM lymphadenitis is made by recovery of the causative organism from lymph node cultures. A simple diagnostic biopsy or incision and drainage of the involved lymph nodes should be avoided, since most of these procedures will be followed by fistulae formation with chronic drainage. However, even with excised nodes with compatible histopathology, only about 50% will yield positive cultures, because in some case these smear-positive, culture-negative cases may be due to fastidious species such as *Mycobacterium haemophilum* or *Mycobacterium genavense*. Approximately 80% of culture-proven cases of NTM lymphadenitis are due to MAC. Its predominance is due to a change approximately from 20-30 years ago, when most geographic areas reported *Mycobacterium scrofulaceum* as the most common etiologic agent, only about 10% of the culture-proved mycobacterial cervical lymphadenitis in children is due to *Mycobacterium avium* complex and *Mycobacterium scrofulaceum*. Also *Mycobacterium haemophilum*, *Mycobacterium malmoense*, *Mycobacterium fortuitum* and others have been isolated from cases of lymphadenitis including HIV patients. In contrast, in adults more than 90% of the culture-proven mycobacterial lymphadenitis is due to *Mycobacterium tuberculosis* 8, 67, 70-76.

7.6 Disseminated disease in immunocompromized individuals

Disseminated disease due to NTM in AIDS patients usually occurs only in those with very advanced immunosuppressant, because these patients frequently have other complications, the diagnosis of mycobacterial infection may be confused or delayed. The diagnosis is exceedingly rare in person with >100 CD4 cells, and it should usually be suspected only in persons with <50 CD4 cells⁵³. MAC have been found to be more commonly isolated from HIV-positive and HIV-negative patients, in their the portal of entry mainly through the gut^{31 67,69}. Persistent high grade fever, night sweats, anemia and weight loss in addition to nonspecific symptoms of malaise, anorexia, diarrhoea, myalgia and occasional painfuladenopathy are common signs and symptoms associated with MAC disease in AIDS cases. Others pulmonary and extrapulmonary mycobacterial infections in AIDS patients are for *Mycobacterium kansasii*, *Mycobacterium scrofulaceum*, *Mycobacterium xenopi*, *Mycobacterium simiae*, *Mycobacterium fortuitum-Mycobacterium chelonae* complex, *Mycobacterium malmoense*, *Mycobacterium szulgai*, and more recently *Mycobacterium genavense*, *Mycobacterium haemophilum* and *Mycobacterium celatum*⁷⁴⁻⁸².

8. Identification of nontuberculous mycobacteria

Traditional identification of NTM, as well as *Mycobacterium tuberculosis*, has relied upon statistical probabilities of presenting a characteristic reaction pattern in battery biochemical test. The niacin test was the most useful for separating NTM and *Mycobacterium tuberculosis* because the former is usually negative, whereas isolates of *Mycobacterium tuberculosis* are positive. Runyon devised the first good scheme for grouping NTM based on growth rates and colony pigmentation. For the diagnostic of NTM is very important to know the growth rates and colony pigmentation, and biochemical test such as, niacin production, nitrate reduction, tween-80 hydrolysis, arylsulphatase, urease, tellurite reduction, catalase

qualitative and quantitative, grown on MaConkey agar, sodium chloride tolerance, etc, are adequate to identify majority of clinically relevant mycobacteria. This strategy is very necessary and important for the diagnostic of NTM, however, some time consuming and is not conclusive for many isolates with variable characters. For this reason others alternative diagnostic techniques are recommended, for example, the analysis of the mycolic acids of mycobacteria by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC), and more recently the identification and characterization of NTM by molecular methods, based on new knowledge about the gene sequences of mycobacteria many gene probes for the identification of isolates as well as amplification of specific gene fragments from the lesions and mycobacterial culture isolates have been developed; gene probes, polymerase chain reaction (PCR) techniques, DNA fingerprinting techniques, etc,^{35-40, 43,44,48, 83, 84}

9. *Mycobacterium tuberculosis* and nontuberculous mycobacteria diseases in the HIV/AIDS patients

After years of worldwide decline of tuberculosis (TB), this disease has returned as a big problem in the Public Health. The resurgence of TB in the past decades is closely linked to acquired immunodeficiency syndrome (AIDS) pandemic. The high susceptibility of patients infected with the human immunodeficiency virus (HIV) to TB and others mycobacterial infections is unique, creating a lot of diagnostic and therapeutic challenges for clinicians^{12,32,24}. Pulmonary tuberculosis is the most common manifestation of tuberculosis in adults infected with HIV^{53,85,86}.

HIV/TB co-infection occurs in various stages of HIV infection, with the clinical pattern correlating with the patient's immune status. In the early stages of HIV infection, when immunity is only partially compromised, the features are more typical of tuberculosis, commonly with upper lobe cavitations, and the disease resembles that seen in the pre-HIV era. HIV-infected patients present with atypical pulmonary disease due to immune deficiency advances, resembling primary tuberculosis or extra pulmonary and disseminated disease, commonly with hilar adenopathy and lower lobe infection⁸⁷.

9.1 Clinical symptoms in pulmonary tuberculosis

The clinical symptoms are severally similar in HIV-infected and HIV-negative patients. However, cough is reported less frequently by HIV-infected patients, probably because there is less cavitations, inflammation and endobronchial irritation as a result of a reduction in cell-mediated immunity. Similarly, haemoptysis, which results from caseous necrosis of the bronchial arteries, is less common in HIV-infected patients^{87,88}.

In general, the traits that characterize HIV-TB co-infection include the potential for rapid progression from primary infection to disseminated disease, atypical radiographic features of pulmonary disease, increased frequency of extrapulmonary disease and involvement of unusual sites of infection. All of these atypical features seem to occur more commonly with more advance stages of immunosuppression and the paradigm that emerges is one of typical TB early in the course of HIV infection and atypical manifestation with advanced HIV disease, in this case the atypical features included lower lobe alveolar opacities, multifocal alveolar opacities, interstitial infiltrates, mediastinal adenopathy and pleural effusions^{24,30,67,69,89}.

9.2 Clinical symptoms in extrapulmonary tuberculosis

The main manifestation of extrapulmonary tuberculosis in AIDS patients are lymphadenopathy, pleural effusion, meningitis, pericardial effusion and miliary tuberculosis. This diagnostic is often difficult because the patients with HIV are prone to all of the usual bacterial and viral infection that affect a non-HIV infected patients, so, the presentation of extrapulmonary tuberculosis in HIV-infected patients is generally no different ^{8, 69}.

9.3 Nontuberculous mycobacterial infection in HIV/AIDS patients

The clinical relevant of NMT infection in HIV/AIDS patients are very frequent, this infection can be pulmonary and extrapulmonary and their symptoms are the same that *Mycobacterium tuberculosis* ^{51-54, 69}. Recently, the nontuberculous mycobacterial are also denominated as environmental opportunist mycobacterial. Normally, they live as environmental saprophytes and they cause opportunist disease in human. Many cases of NTM are associated with some form of immune deficiency in special HIV/AIDS patients. In this group of patients is frequently to find this mycobacterial species as etiological agent for this reason is very important their microbiology diagnostic which is different to *Mycobacterium tuberculosis* ^{90, 91}.

Disseminate *Mycobacterium avium complex* (MAC) diseases was one of the first opportunist infections recognized in the syndrome of AIDS since 20 years ago. The interest of the diagnostic of disseminated MAC and others species of nontuberculous mycobacteria infection have been increased as a result of the HIV pandemic. The prevention and treatment in nontuberculous mycobacteria are life long because cure of them were not achievable in AIDS patients with profound immune suppression. The precise immune defect predisposing HIV/AIDS patients to disseminated diseases is unknown ⁹².

The main manifestation of pulmonary and extrapulmonary infections for *Mycobacterium tuberculosis* and nontuberculous mycobacterial are the same affecting lung, pleura, skin, lymphatic system and producing dissemination infection (Figure 1, Figure 2), (Figure 3A-3B-3C, Figure 4A-4B) ^{8, 63, 69}. For this reason is very important the highly active antiretroviral therapy (HAART) for treatment of AIDS patients that has been associated with a market reduction in the incidence of most opportunistic infection ^{82, 89, 92}.

So, is very important that the mycobacteriology laboratory should give a definitive diagnostic, because in immunosuppressed patients is important to find resistant alcohol acid bacillus in order to detect the co-infection with *Mycobacterium tuberculosis* which is the most frequently agent found. Nevertheless, others species of mycobacteria may be causing infection and should be search for.



Fig. 1. Mesenteric lymph nodes for *Mycobacterium tuberculosis* in AIDS patients.



Fig. 2. Biopsy of liver pedicle lymph nodes for *Mycobacterium tuberculosis* in AIDS patients.



Fig. 3. AIDS patients with skin lesions from *Mycobacterium avium* complex (Figure 3A, Figure 3B) and *Mycobacterium fortuitum* (Figure 3C)

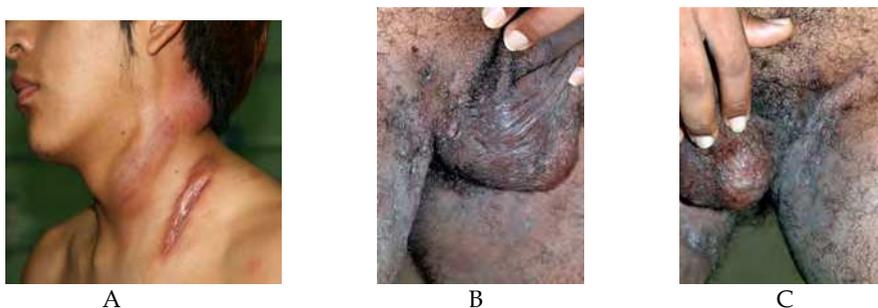


Fig. 4. Lymphadenitis cervical from *Mycobacterium tuberculosis* (Figure 4A), inguinal-testes lesions from *Mycobacterium avium* complex in lymphatic system (Figure 4B, Figure 4C).

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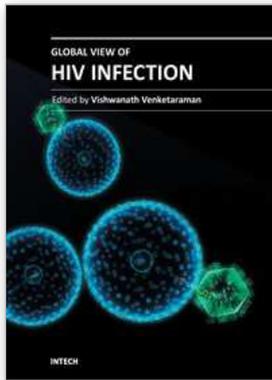
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